Docket No.: 0020-4559P
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Eijiro WATANABE et al.

Application No.: 09/301,766 Confirmation No.: 6045

Filed: April 29, 1999 Art Unit: 1638

For: RAFFINOSE SYNTHASE GENES AND THEIR USE Examiner: D. H. Kruse

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

As required under § 41.37(a), this brief is filed more than two months after the Notice of Appeal filed in this case on December 22, 2006, and is in furtherance of said Notice of Appeal.

The fees required under § 41.20(b)(2) are addressed in the accompanying TRANSMITTAL OF APPEAL BRIEF.

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BRIEF ON BEHALF OF APPELLANT

I. REAL PARTY IN INTEREST

The Assignee of the present application is Sumitomo Chemical Company, Ltd. of Osaka, Japan.

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

An Appeal Brief was filed in the copending application no. 08/992,914 on December 26, 2006. An Examiner's Answer has been received and a Reply Brief filed July 16, 2007 in that application.

The copending '914 application is directed to similar subject matter as the present application and the appeal is of the same ground of rejection. That is, both the '914 and the present application present for appeal the question of whether or not a certain degree of sequence identity of a gene or protein sequence is sufficient to establish by the preponderance of the evidence an asserted utility for an invention, and corresponding adequacy of written description and enablement of "how to use" the invention.

III. STATUS OF CLAIMS

The following is the status of the claims as of the mailing of the Final Office Action on August 23, 2006:

Claims 1, 4-10, 16-23, 28 and 29 are pending in the application.

Claims 6 and 7 are indicated as "objected to" in the Office Action Summary and indicated as "allowed" in the Conclusion of the Office Action (paragraph 6 on page 9). Claims 6 and 7 are independent claims and so Appellants suppose that the correct status of claims 6 and 7 is "allowed."

The Examiner's decision rejecting claims 1, 4, 5, 8-10, 16-23, 28 and 29 has been appealed.

Claims 1, 4, 5, 8-10, 16-23, 28 and 29 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support in the specification and also for alleged lack of enablement by the disclosure of the specification.

IV. STATUS OF AMENDMENTS

No further amendments or arguments have been filed pursuant to the Final Office Action of August 23, 2006.

V. SUMMARY OF CLAIMED SUBJECT MATTER

References to page numbering of the specification are made herein to the specification as originally filed. Support for each limitation in the claims is interlineated into the claim in **bold**.

1. An isolated nucleic acid which comprises a polynucleotide encoding a protein that binds a D-galactosyl group through the α(1→6) bond to the hydroxyl group attached to the carbon atom at 6-position of the D-glucose residue in a sucrose molecule to form raffinose **(page 2, lines 7-13 and also at page 31, line 22 to page 32, line 4)**, wherein said polynucleotide comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NO: 3 **(page 4, lines 20-21)**,

(b) a nucleotide sequence depicted by the 236th to 2584th nucleotides in the nucleotide sequence as depicted in SEQ ID NO: 4 **(page 4, lines 23-25)**,

(c) a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NO: 5 **(page 4, lines 2-3)**,

(d) a nucleotide sequence depicted by the 134th to 2467th nucleotides in the nucleotide sequence as depicted in SEQ ID NO: 6 **(page 4, lines 5-7)**,

(e) a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NO: 7 **(page 4, lines 9-10)**,

(f) a nucleotide sequence depicted by the 1st to 1719th nucleotides in the nucleotide sequence as depicted in SEQ ID NO: 8 **(page 4, lines 12-13)**,

(g) a nucleotide sequence obtained from a polynucleotide which is amplified from a nucleic acid obtained from beet with a combination of a PCR primer selected from the group consisting of SEQ ID NO: 11 and SEQ ID NO: 13 and a PCR primer selected from the group consisting of SEQ ID NO: 12 and SEQ ID NO: 14, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of (a) or (b), in a buffer comprising 0.9M NaCl and 0.09M citric acid at 65°C to 68°C **(Example 4 beginning at page 42,**

line 10 (as to isolation of a cDNA from beet using PCR). The particular primers of SEQ ID NOS: 11-14 are described in "List 2" at page 13, line 12 and use of these primers to obtain a full length coding sequence of a raffinose synthase cDNA from beet is described at page 53, lines 1-9. The particular Sequence Listing Identifiers correspond to sequences in the Sequence Listing. Hybridization conditions recited in the claim are set forth at page 18, lines 5-10.), and

(h) a nucleotide sequence obtained from a polynucleotide which is amplified from a nucleic acid obtained from mustard or rapeseed with a combination of a PCR primer selected from the group consisting of SEQ ID NO: 15, SEQ ID NO: 17 and SEQ ID NO: 19 and a PCR primer selected from the group consisting of SEQ ID NO: 16, SEQ ID NO: 18 and SEQ ID NO: 20, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of any one of (c) to (f), in a buffer comprising 0.9M NaCl and 0.09M citric acid at 65°C to 68°C **(Examples 6 and 7 beginning at page 45, line 15. The particular primers recited in the claim are described in "List 3" at page 15, line 22 to page 16, line 3, and these primers are described as useful for isolating a cDNA of the complete coding portion of a raffinose synthase gene from mustard or rapeseed at page 53, line 14 to page 54, line 14. The particular Sequence Listing Identifiers correspond to sequences in the Sequence Listing. Hybridization conditions recited in the claim are set forth at page 18, lines 5-10.)**.

4. An isolated nucleic acid comprising a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NO: 3. **(page 4, lines 20-21 and Sequence Listing originally filed (and re-filed with a Preliminary Amendment on April 29, 1999))**

5. An isolated nucleic acid comprising the nucleotide sequence depicted by the 236th to 2584th nucleotides in the nucleotide sequence as depicted in SEQ ID NO: 4. **(page 4, lines 23-25 and Sequence Listing originally filed (and re-filed with a Preliminary Amendment on April 29, 1999))**

6. (Allowed) An isolated nucleic acid comprising a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NO: 5. **(page 4, lines 2-3 and Sequence Listing originally filed (and re-filed with a Preliminary Amendment on April 29, 1999))**

7. (Allowed) An isolated nucleic acid comprising the nucleotide sequence depicted by the 134th to 2467th nucleotides in the nucleotide sequence as depicted in SEQ ID NO: 6. **(page 4, lines 5-7)and Sequence Listing originally filed (and re-filed with a Preliminary Amendment on April 29, 1999))**

8. An isolated nucleic acid comprising a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NO: 7. **(page 4, lines 9-10 and Sequence Listing originally filed (and re-filed with a Preliminary Amendment on April 29, 1999))**

9. An isolated nucleic acid comprising the nucleotide sequence depicted by the 1st to 1719th nucleotides in the nucleotide sequence as depicted in SEQ ID NO: 8. **(page 4, lines 12-13 and Sequence Listing originally filed (and re-filed with a Preliminary Amendment on April 29, 1999))**

10. An isolated nucleic acid comprising the nucleotide sequence as depicted in SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8. **(page 5, lines 14-16 and Sequence Listing originally filed (and re-filed with a Preliminary Amendment on April 29, 1999))**

16. An isolated nucleic acid comprising the nucleic acid of claim 1, which is operatively linked to a promoter. **(page 6, lines 15-19)**

17. A vector comprising the nucleic acid of claim 1. **(page 6, lines 19 to 20)**

18. A transformant, wherein the nucleic acid of claim 1 is introduced into a host cell. **(page 6, lines 21-23)**

19. A transformant, wherein the nucleic acid of claim 16 is introduced into a host cell. **(page 6, lines 24-25)**

20. A transformant, wherein the vector of claim 17 is introduced into a host cell. **(page 7, lines 1- 2)**

21. The transformant of claim 18, wherein the host cell is a microorganism. **(page 7, lines 3-6)**

22. The transformant of claim 18, wherein the host cell is a plant cell. **(page 7, lines 5-6)**

23. A method for producing a raffinose synthase which comprises the steps of:
culturing or growing the transformant of claim 18 to produce the raffinose synthase, and
collecting the raffinose synthase. **(page 32, lines 4-20. Purification of raffinose synthase from plants is known in the art, for example as described by Lehle et al. cited at the bottom of page 31.)**

28. The nucleic acid of claim 16, wherein said promoter is effective in a plant cell. **(page 29, line 24 to page 30, line 12)**

29. The nucleic acid of claim 16, wherein said promoter is effective in a yeast cell. **(page 29, lines 22-23)**

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds of rejection are to be reviewed on appeal:

Claims 1, 4, 5, 8-10, 16-23, 28 and 29 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support in the specification and also for alleged lack of enablement by the disclosure of the specification. (As stated in the Final Office Action at paragraph 4 on page 2 and at paragraph 5 at page 6.)

VII. ARGUMENT

VIIA. Rejections Under 35 U.S.C. § 112, first paragraph – written description

VIIA.1. Claim 1

Claim 1 is rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support of the claimed invention. Appellants respectfully submit that this rejection should be reversed.

In the Final Office Action of August 23, 2006, the Examiner makes a few different assertions regarding the written description requirement. First he states that, as to SEQ ID NO: 7 (note polynucleotides (e) and (f)), description of an incomplete coding sequence does not describe a nucleic acid sequence encoding a raffinose synthase enzyme and that the specification includes no description of the portions of the amino acid sequence necessary for raffinose synthase activity. Second, as to nucleic acids isolated from "beet" or "mustard or rapeseed" (note polynucleotides (g) and (h)), the Examiner asserts that, "merely describing a method by which a nucleic acid may be isolated does not describe the nucleic acid encoding a raffinose synthase as asserted by Applicant." Third, as to SEQ ID NO: 3, and presumably applicable to all of polynucleotides (a), (b) and (e) through (h)[1], the Examiner asserts that a demonstration of the biological activity (and thus of utility) for a protein of a particular amino acid sequence cannot be used to support an assertion of similar activity for a protein of similar sequence.

There are no "bright line" tests for whether or not a specification provides adequate written description of a claimed invention. The Examiner must carefully review the claims, and carefully review the specification to determine whether, in view of what is known in the art at the time the application was filed, the specification provides evidence that the inventor was in "possession" of the invention as claimed. *Capon v. Eshhar,* 76 USPQ2d 1078 (Fed. Cir. 2005); *Faulkner v. Inglis,* 79 USPQ2d 1001 (Fed. Cir. 2006).

[1] The polynucleotides of (c) and (d) are allowed as claims 6 and 7.

As to the Examiner's first assertion, SEQ ID NO: 7 (encoded by nucleotides 1 to 1719 of SEQ ID NO: 8) is indeed only a partial sequence of a raffinose synthase; about 25% of the full-length sequence is missing from the amino-terminal end. However, the instant claim 1 does not recite that the claimed polynucleotide "consists of" the recited sequence. Rather, the claim recites that the polynucleotide "comprises" the recited polynucleotide, and hence also includes any amino acids necessary to complete an amino acid sequence of a raffinose synthase protein. Two such complete amino acid sequences are disclosed in the present application as SEQ ID NOS: 3 and 5. Methods for determining the complete nucleotide sequence of a cDNA encoding raffinose synthase from rapeseed are explained in the specification, as used to obtain complete sequences are obtained for examples from beet and mustard. Alternatively, one of ordinary skill in the art might simply obtain the missing portion of the enzyme from the complete cDNAs for these two proteins that are described (SEQ ID NOS: 2 and 4). The Board is reminded that claim 1 specifically includes as a feature that the encoded protein exhibit a recited enzymatic activity, and so inoperable embodiments are excluded from the claim.

From the above, it is clear that the specification evidences that the inventors had in their possession the invention claimed in claim 1, parts (e) and (f). The Examiner has merely stated a summary conclusion, parroting guidelines to the effect that the specification must set forth an explicit "structure-function relationship"[2] used by the USPTO to implement a policy restricting cloned gene inventions to specifically disclosed species, rather than carefully considering the facts presented by the instant application and claims as required by Federal Circuit case law.

Notwithstanding the failure of the Examiner to carefully consider the facts of the present application, he is simply wrong that the specification does not explain parts of the RFS sequence that should be preserved for activity. The specification explains that certain portions of the amino acid sequence of a RFS should be constrained to high homology to SEQ ID NO: 3 or to SEQ ID NO: 5. See, pp. 20-21, indicating portions of high homology (accounting for both sequences) from amino acids 103 to 213, 255 to 275, 289 to 326 and 609 to 696.

[2] See, pp. 3-4 of the Office Action mailed March 1, 2005, referenced in the Office Action of December 2, 2005, as the "previous Office Action" addressing this issue.

As to the Examiner's second assertion, Federal Circuit case law makes abundantly clear that it is permissible for an Applicant to claim an invention in product-by-process terms. *See, e.g. Enzo Biochem, Inc. v. Gen-Probe, Inc.,* 63 USPQ2d 1609 (Fed. Cir. 2002) and *Fiers v. Revel,* 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The Examiner's position with respect to parts (g) and (h) of claim 1 is simply complete legal error.

The Examiner's third argument is in the first place more related to the issue of enablement of the utility of the invention than to the written description of the structure of the invention. More substantively, the Examiner's third argument is contrary to the substantial evidence in the record of the present application. The present specification describes in detail a method for cloning raffinose synthase (RFS) genes from plants of broadly diverse genera (*Glycine, Beta, Brassica*). The specification describes using sequence information of a cDNA encoding part of a RFS from *Glycine max* (SEQ ID NO: 2) to prepare a set of PCR primers that will hybridize to a degenerate set of sequences[3] that are used to amplify mRNA obtained from other plants and so isolate fragments of RFS cDNA. These initial amplification products are sequenced, then that further data are used to prepare a new set of primers specific for RFS for the particular plant being studied. The second set of primers is used to make new amplification products that are cloned and from which the complete sequence of the cDNA is obtained (*see,* the Examples 1-6 of the specification). This approach was used three times in working examples of the present specification to successfully obtain RFS cDNAs from three different plants. The complete coding portions of the cDNA for *Beta vulgaris* and *Brassica juncea* (SEQ ID NOS: 4 and 6, respectively) and part of the coding portion of a cDNA from *Brassica napus* (SEQ ID NO: 8) are presented. Appellants have presented evidence in the form of a Declaration of Dr. Watanabe that demonstrates unequivocally that a protein having the amino acid sequence of SEQ ID NO: 5 has biological activity of a RFS, and this is not disputed by the Examiner[4]. Therefore, plainly the approach described in the specification can be used successfully to isolate a cDNA encoding RFS from diverse genera of plants.

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[3] The primers used for initial amplification include degenerate positions or inosine bases that recognize A/G or C/T alternatives.

[4] Claims 6 and 7, directed to this embodiment (also represented by (c) and (d) in claim 1) are allowed.

The Examiner asserts that one of ordinary skill in the art is not able to distinguish RFS enzymes from the closely related stachyose synthase enzymes, and therefore the actual biochemical activity of the proteins encoded by the cDNAs of SEQ ID NOS: 4 and 8 remain unknown. Accordingly, the Appellants are asserted to have provided only one example of a RFS-encoding cDNA and therefore, except for the claims directed to the species having proven activity, the written description of the invention is inadequate.

RFS enzymes are a subfamily of enzymes grouped together with the subfamily of stachyose synthases (STS) in a family of glycoside hydrolase enzymes. Appellants have presented substantial evidence that one of ordinary skill in the art can distinguish RFS from STS members of the glycoside hydrolase family. This evidence is in the form of the data in Tables 1 and 2 and Figure 1 presented with Appellants' Amendment filed February 11, 2004 and in Table 3 and Exhibit 1 presented with Appellants' Amendment filed November 15, 2004. These data, and the Exhibit supporting the robustness of the analysis, show that RFS enzymes are distinguishable from STS enzymes by determination of the degree of sequence identity to SEQ ID NO: 1, 3, 5 or 7 according to the present specification. In particular, the data show that RFS enzymes among themselves are at least 50% identical at the amino acid level, and that STS enzymes are similarly homologous to each other (actually a bit more so, about 65%). However, the degree of identity between RFS and STS enzymes is at most about 45%. Sequence identity analysis permits the artisan of ordinary skill to illustrate the distinction between RFSs and STSs by a "dendrogram", as shown in Figure 1 attached to the Amendment filed February 11, 2004.

Furthermore, Appellants have argued that the specification of the copending application 08/992,914, which discloses additional examples of RFS cDNAs cloned essentially in the manner described in the present specification, provides another example in which biological activity of a RFS cDNA[5] is demonstrated, and that this demonstration further evidences the effectiveness of the methods described in the present specification in obtaining cDNAs encoding RFS proteins. (*See,* Appellants amendment of June 2, 2006, at page 8, lines 3 ff.) The Examiner

[5] from *Vinca faba*, SEQ ID NO: 1 of the '914 application.

has so far dismissed this further evidence because, "each application is to be considered on its own merits." (*See,* page 5, lines 17-18 of the Final Office Action.) That may be the case, but the facts of the existence of the '914 application and its working examples may be considered as evidence in this application.

In order to meet the requirements for adequate written description, the specification must provide evidence that the inventors "possessed" the invention as claimed at the time the application was filed. *Vas-Cath v. Murhurkar* 19 USPQ2d 1111 (Fed. Cir. 1991). The evidentiary standard that must be met by Appellants is only that of the preponderance of the evidence. *See, In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The Examiner seems to be improperly requiring that Appellants meet a higher evidentiary burden, *i.e.* "clear and convincing" evidence or even "beyond reasonable doubt."

Appellants submit that the evidence of record in the present application firmly establishes that it is "more likely than not" that all of the sequences disclosed in the present application are those of RFS enzymes. This has been unequivocally established by biochemical assay for one disclosed sequence, and sequence similarity as analyzed by one of ordinary skill in the art establishes that it is more likely than not true for the others. Furthermore, the same approach for cloning RFS-encoding cDNAs used in the present application has been further applied by the Appellants, as described in a copending application, and yet a further demonstration that the approach obtains cDNA encoding an RFS enzyme, as determined by assay of another expressed cDNA, has been made.

Appellants submit that the present specification, by showing reduction to practice of four species of the claimed invention obtained from three diverse genera of plants, adequately evidences that the inventors "had possession" of the claimed invention at the time the present application was filed. Accordingly, the decision of the Examiner that claim 1 is not supported by adequate written description in the specification should be **reversed**.

VIIA.2. Claims 4 and 5

Claim 4 of the present application is directed to an isolated nucleic acid comprising a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 3. Claim 5 recites a specific polynucleotide sequence of SEQ ID NO: 4 from which SEQ ID NO: 3 is derived. SEQ ID NO: 3 is the amino acid sequence of the complete coding region of a cDNA obtained from a Chenopdiaceae plant (*Beta vulgaris*) in Examples 3 and 4. As the sequence is of a complete protein coding portion of the cDNA, the rejection of these claims is based only upon the argument of the Examiner regarding the evidence that the encoded enzyme has RFS activity.

Appellants have explained above that there is substantial evidence in the record that establishes at least to the preponderance of the evidence standard that the amino acid sequence of SEQ ID NO: 3, encoded by the cDNA of SEQ ID NO: 4, represents a protein having RFS activity. The particular amino acid sequences in question were determined by a cloning method generally accepted in the art as useful for cloning functionally homologous proteins across species lines.

Finally, claims 4 and 5 recite specific sequences at either the nucleotide or amino acid level. In either case, the skilled artisan can readily determine the exact structure or family of structures encompassed by the claims and so there is no question that the inventors "possessed" the inventions described in these two claims.

For all of the above reasons, the rejection of claims 4 and 5 under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description in the specification, should be **reversed**.

VIIA.3. Claims 8 and 9

Claim 8 of the present application is directed to an isolated nucleic acid comprising a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 7. Claim 9 recites a specific polynucleotide sequence of SEQ ID NO: 8 from which SEQ ID NO: 7 is derived. SEQ

ID NO: 7 is the amino acid sequence of part of the coding region of a cDNA obtained from a Cruciferae plant (*Brassica napus*) in Examples 6 and 7.

Among the arguments presented by the Examiner against claim 1, only the issues of a partial sequence and the sufficiency of the evidence that a RFS enzyme is encoded are applicable to claims 8 and 9.

Appellants have explained above that claims 8 and 9 are directed to nucleic acids comprising the recited sequences, and thus may include additional nucleotides encoding further amino acids as may be necessary to provide an enzyme having RFS activity. Appellants have explained previously that the specification provides description of two complete RFS enzyme amino acid sequences, and that these data can be used to prepare the additional sequences for attachment to the partial sequence of SEQ ID NO: 7. The specification also describes regions of high homology that should be present in an enzyme having RFS activity. For the convenience of the Board, Appellants present as Exhibit 4 attached hereto an alignment of the amino acid sequences of SEQ ID NO: 7 (sc-07) at issue with SEQ ID NO: 5 (sc-05), which represents a protein demonstrated by biochemical assay to have activity as a raffinose synthase.[6] In the alignment, identical amino acids are shown by *. The regions of high homology within raffinose synthases described in the specification are indicated by the shaded portions of the sequence. Appellants submit that the missing 4% of that region (or for that matter the entirety of the missing amino-terminal portion) may be supplied by the corresponding amino-terminal end sequences of SEQ ID NO: 3 or 5 as desired by the practitioner of the invention.

Appellants have also explained above that the evidence of record in the present application is sufficient, at least to the standard of the preponderance of the evidence, to establish that the amino acid sequence of SEQ ID NO: 7 is that of a RFS enzyme.

[6] Appellants submit that Exhibit 4 does not constitute "new evidence" as it merely presents data actually present in the record in the form of SEQ ID NOS: 5 and 7 and otherwise described in the specification. However, Exhibit 4 presents this information in a different format convenient for consideration by the Board.

Finally, claims 8 and 9 recite specific sequences at either the nucleotide or amino acid level. In either case, the skilled artisan can readily determine the exact structure or family of structures encompassed by the claims and so there is no question that the inventors "possessed" the inventions described in these two claims.

For the reasons above, the decision of the Examiner rejecting claims 8 and 9 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description support by the specification, should be **reversed**.

VIIA.4. Claim 10

Claim 10 is directed to an isolated nucleic acid comprising the entirety of SEQ ID NO: 4, SEQ ID NO: 6 or SEQ ID NO: 8. The scope of claim 10 differs slightly from that of claims 5, 7 and 9 in that the entire length of the recited nucleotide sequence is recited in claim 10. In contrast, claims 5, 7 and 9 recite the coding portions of the nucleotide sequences.

Appellants's arguments above apply to claim 10 as well.

Claim 10 recites a group of specific structures that are expressly stated in the Sequence Listing as originally filed. There can be no doubt that the specification describes these sequences exactly and so no doubt that claim 10 meets the requirement for written description of the claimed invention.

For the reasons above, the decision of the Examiner rejecting claim 10 under 35 U.S.C. § 112, first paragraph, for lack of adequate written description support by the specification, should be **reversed**.

VIIA.5. Claims 16-23, 28 and 29

Claims 16-23, 28 and 29 are dependent ultimately from claim 1 and stand rejected for the same reasons as claim 1 is rejected. These dependent claims are directed to embodiments of the invention in which a nucleic acid providing a sequence encoding a RFS enzyme is operatively

linked to a promoter (claim 16) or placed into a vector (claim 17) or to a transformed host cell comprising the nucleic acid of claim 1 either *per se,* or as part of a promoter-structural gene construct or as part of a vector (claims 18, 19 and 20, respectively). Claims 22, 23, 28 and 29 further define the nature of the host cell or the nature of the promoter, respectively.

The Examiner has so far presented no reason for rejection of claims 16-23, 28 and 29 independent from the rejection of claim 1. Thus, the Board is respectfully requested to consider that, should the decision of the Examiner with respect to any part (a) through (h) of claim 1 be reversed, the dependent claims 16-23, 28 and 29 should be indicated as allowable if rewritten to recite the allowable part of claim 1.

VIIB. Rejections under 35 U.S.C. § 112, first paragraph – enablement

Claims 1, 4, 5, 8-10, 16-23, 28 and 29 stands rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement of the claimed invention by the disclosure of the specification. The Examiner's position on this issue is essentially that grouping of enzyme primary structures into families based upon sequence identity is insufficient to support an assertion that a protein of unconfirmed activity will have the activity ascribed to that family demonstrated by biochemical assay of at least one of its members. The Examiner therefore asserts that the present specification is enabling of "how to use the invention" only for those proteins for which activity as a raffinose synthase is actually demonstrated by biochemical assay. In the present instance, the Examiner asserts that the claims must be limited with respect to the amino acid sequence of the enzyme to SEQ ID NO: 6, which is the sole amino acid sequence described in the present specification for which raffinose synthase activity has been actually demonstrated.

Appellants disagree.

VIIB.1. Claim 1

The question of enablement is to be considered under a multifactor analysis as set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). It is incumbent upon the Examiner to first establish a *prima facie* case for lack of enablement. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (holding examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). Should the Examiner do so, then the Appellant must establish, by the preponderance of the evidence, that no undue experimentation is required to practice the invention as claimed. *In re Oetiker*, 24 USPQ2d at 1444.

Appellants first submit that the Examiner has never established a proper *prima facie* case for lack of enablement of the claimed invention. Proper analysis of the question of enablement requires that the factors of 1) the breadth of the claims, 2) the nature of the invention, 3) the level of ordinary skill in the art, 4) the amount of experimentation needed, 5) the state of the art at the time the invention was made, 6) the amount and quality of guidance provided by the specification, 7) the presence or absence of working examples and 8) the predictability in the art. Of these factors, the Examiner repeatedly has only addressed the predictability in the art. The Examiner's position is that, because there is evidence in the record for RFS activity only for a protein of amino acid sequence of SEQ ID NO: 5, and the degree of sequence identity among the amino acid sequences identified in the working examples is as low as 50%, Appellants cannot reliably assign the biochemical activity of a raffinose synthase to the amino acid sequences of SEQ ID Nos: 3 and 7.

Applicants note first that analysis of enablement is a question of whether "undue experimentation" is required to practice the invention throughout its claim scope. Consideration of the question of undue experimentation is by weighing all of several factors enumerated in *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988).

The Examiner fails to meet his burden of establishing a *prima facie* lack of enablement. The Examiner's analysis of the question of undue experimentation looks only at the factor of

whether working examples of the claimed invention are described in the specification and an assertion that it is unpredictable whether any particular nucleic acid produced according to the teachings of the invention would in fact exhibit raffinose synthase activity. This analysis is legally insufficient to establish *prima facie* lack of enablement, as the Examiner fails to consider the breadth of the claims, the nature of the invention, the level of ordinary skill in the art, the quantity of the experimentation needed, the guidance provided by the specification (other than the presence or absence of working examples) and the state of the art at the time the invention was made. Furthermore, the kind of predictability, *a priori* knowledge of functionality of the enzyme obtained using the methods of the invention, is not the kind of predictability envisioned by the Court in *Wands.* The instant rejection cannot properly be sustained against claim 1.

The nature of the invention and the breadth of the claims

The claimed invention relates to isolated nucleic acids that encode an enzyme having a defined biological activity. As to claim 1, the invention as most broadly stated (*e.g.* (g) or (h)) lies in a nucleic acid that is defined by (1) inclusion of at least certain sequence features (that is, the PCR primer sequences that are used to generate the claimed nucleic acid), (2) hybridization to a certain reference sequence and (3) encoding a protein having a defined enzymatic activity. Claim 1 includes narrower definitions (a) through (f), related to particular amino acid sequences. Among descriptions (a) through (f), the nucleic acid as described by amino acid sequence SEQ ID NO: 5 ((c) and (d)) is proven to encode a protein having RFS activity, the nucleic acid described by reference to SEQ ID NO: 3 ((a) and (b)) represents the entire coding sequence of a RFS protein and the nucleic acid described by reference to SEQ ID NO: 7 ((e) and (f)) represents about 70% of the length of the coding sequence of a RFS protein.

Inoperative embodiments are excluded from the claims by the requirement that the encoded protein have RFS activity.

The art of molecular biology, in particular the art of expression of recombinant proteins, is one in which the artisan of ordinary skill expects to perform a few weeks or months of experimentation in generating variants of a protein, then isolating clones encoding those

variants and then (perhaps) re-cloning the isolated variants into vectors for expressing a protein, and then screening expressed proteins for activity.

The level of ordinary skill in the art

The artisan of ordinary skill in the art of cloning and expressing recombinant proteins is generally accepted as one having a Ph.D. degree and perhaps higher *i.e.*, having significant post-doctoral laboratory experience. Such a person is skilled in the design and performing of experiments for isolating DNA clones and for screening them for a desired property, for example encoding a protein having a particular activity.

The amount of experimentation needed

The amount of experimentation needed to practice the present invention is not unduly large or burdensome. The practitioner must isolate a template genomic DNA or RNA from an organism, perform a polymerase chain reaction using primers described in the specification to generate an amplified fragment, clone that fragment into an expression vector, express the encoded protein and then screen the protein for activity as a raffinose synthase. All of these steps are either well-known in the art or described in detail in the specification (*e.g.* pp. 31-33 (bacterial expression of the cloned cDNA and assay for RFS activity and Examples 1-6 beginning at p. 38) and furthermore are expected to be performed by the artisan of ordinary skill.

The state of the art at the time the invention was made

At the time the invention was made, the state of the art of molecular biology was such that the various laboratory operations that must be performed to carry out the experimentation required to practice the instant invention, *i.e.* cloning of DNA molecules and expressing them in a host cell, were routine. Also, polymerase chain reaction amplification of nucleic acids was routine.

The raffinose content of a number of organisms, especially including plants and some algae, was known. The biochemistry of raffinose synthesis in plants had been established, and the role of raffinose synthases as rate-limiting of raffinose production was known. (*See, e.g.* pp. 1-2 of the specification.)

A biochemical assay for raffinose synthase activity was described. See Lehle et al., *Eur. J. Biochem.* 38:103 (1973) (attached).

The guidance provided by the specification including the presence or absence of working examples

The specification provides ample guidance to the skilled artisan for practicing the invention broadly. In particular, the specification discloses in detail how to clone DNAs encoding putative raffinose synthase enzymes. The specification provides details such as organisms likely to be useful for isolating template genomic DNA or RNA from plants commensurate in scope with claim 1 and corresponding PCR primers (Chenopdiceae (for beet), p. 11, line 14; Cruciferae (for mustard and rapeseed), p. 13, line 18 and associated PCR primers in Lists 2 and 3).[7] The specification describes methods for cloning DNA encoding a putative raffinose synthase enzyme from an RNA fraction, including an extensive list of primers that can be utilized for PCR amplification from templates obtained from different organisms (*see, e.g.* Lists 6 and 7 at p. 43; Lists 8 and 9 at page 46; List 10 at p. 47). The specification describes methods for expressing the cloned DNA in plant cells and in bacteria (*see, e.g.* pages 29 to 37). The specification describes a biochemical assay for raffinose synthase, referring to the Lehle article noted above and summarizing the procedure beginning at the bottom of page 31.

The specification also provides a number of working examples of isolation of partial or complete raffinose synthase genes from a number of different plants (*see*, Examples 1-7) and of creation of an expression vector for use in plants (Example 8) transformation of a plant (mustard) with a cloned DNA encoding a raffinose synthase (Example 9).

[7] The specification also includes information useful for obtaining RFS cDNA from soybean.

The predictability in the art

The Examiner asserts that the art of recombinant DNA cloning and recombinant protein expression is unpredictable. The Examiner argues that a practitioner of the invention must engage in trial and error experimentation to identify cloned DNAs that encode functional raffinose synthase genes.

The Examiner's argument is simply incorrect. First, the skilled artisan can follow detailed teachings in the specification of how to clone, express and evaluate DNAs that are likely to encode functional raffinose synthase enzymes. It is true that it is a bit unpredictable whether any individual clone made in an experiment will include a DNA encoding a functional enzyme, but it is not unpredictable whether the skilled artisan would succeed in identifying at least one functional DNA in an experiment as a whole. To the contrary, it is very likely that the skilled artisan would find a cloned DNA encoding a functional enzyme by following the teachings of the specification. Appellants note that the experimental approach described in the specification resulted in identification of four cDNAs described in this application and additional cDNAs as described in the copending '914 application.

The Board might consider certain details from the *Wands* case. In *Wands*, an invention related to isolation of hybridomas that secreted a particular antibody was deemed broadly enabled despite that extensive screening of many cloned cell lines was necessary AND that the success rate of the screening was only 2.8%, including experiments that failed to generate any operable clones at all. The *Wands* panel expressly stated that experimentation, such as the cloning and screening experiments described in the present application, that is expected to be performed by the artisan of ordinary skill, is not undue experimentation.

Applicants submit that a proper weighing of the *Wands* factors will lead the Board to a proper conclusion that no undue experimentation is required to practice the present invention as claimed in claim 1. Accordingly, the Examiner's decision rejecting claim 1 for lack of enablement should be **reversed** because the Examiner failed to establish a *prima facie* lack of enablement.

Furthermore, Appellants have provided evidence, in the form of the Watanabe Declaration attached to their Amendment of February 11, 2004, to support an assertion that the procedures described in the specification result in cloning of cDNAs encoding RFS enzymes. Appellants have also provided evidence that one of ordinary skill in the art can readily distinguish a RFS from a STS or another class of closely related proteins, Seed Imbibation Proteins (SIPs). The data in Figure 1 attached to Appellants' Amendment of February 11, 2004, and submitted as part of the Nagasawa Declaration (copied from the '914 appplication file and submitted with Appellants' Amendment of June 2, 2006) demonstrates unequivocally that the RFS subfamily of glycoside hydrolases (see Appellants' discussion of Peterbauer et al., below) is easily distinguished from the STS or SIP subfamilies of glycoside hydrolases on the basis that RFSs are more similar to each other, and STSs are more similar to each other, than RFSs are similar to STSs. This relationship among their amino acid sequences can be used to construct a "molecular phylogenetic tree" upon a branch of which any particular amino acid sequence thought to represent a RFS or STS (or SIP) can be placed. The Nagasawa Declaration further explains that this analysis is robust in its conclusions (though perhaps the specific degrees of sequence similarity may vary) to three different approaches to sequence similarity analysis.

The Examiner has attempted to support his position regarding unpredictability in the art with evidence from the scientific literature. The Examiner has cited Richmond et al. *Plant Physiology* (2000) and Duggleby, *Gene* (1997) for a general assertion that, "The art teaches that one of skill in the art cannot assume the function of the polypeptide encoded by an isolated nucleic acid solely based on sequence similarity to a known polypeptide sequence. The Examiner cites Peterbauer et al., *Planta* (2002) for the proposition that RFS enzymes have high sequence homology to STSs and SIPs. The Examiner cites Peterbauer et al., *Planta* (1999) for the proposition that their group was the first to isolate a nucleic acid encoding a STS protein. See, the Office Action of August 11, 2003 at p. 3. The Examiner cites Bowie et al., *Science* (1990) for the proposition that it is the three dimensional structure of an enzyme that confers its activity and that folding of a protein can be sensitive to minor changes in sequence. The Examiner cites Lazar *Mol. Cell. Biol.* (1998) as an example of an instance in which a certain change in sequence to TGF-α had no effect on the protein, but another instance of amino acid

substitution "sharply reduced biological activity". The Examiner cites Broun et al., *Science* (1998) for the proposition that a few amino acid substitutions can have radical effects on the activity of an enzyme. *See,* the Office Action of November 20, 2002, at pp. 6-7.

Appellants do not dispute the general conclusion reached from the Bowie, Lazar and Broun papers that it is the three-dimensional structure of a protein that confers its biological activity, or that sometimes there are particular amino acids that must be conserved in the linear sequence to preserve the correct folding of the protein, or even that in some instances two distinct enzymes will share extensive portions of amino acid sequences. These concepts are well-known to the molecular biologist of ordinary skill in the art and they do suggest that it is somewhat unpredictable whether mutating a protein will result in maintaining, lessening or improving its biological activity. However, this is not determinative of whether undue experimentation is required to practice the instant invention. All that such unpredictability establishes is that, without actual assay data, one cannot say beyond reasonable doubt that a mutated protein will retain its original activity. However, this is not the proper standard of evidence to consider during patent prosecution. Appellants' burden is to only establish that <u>it is more likely than not</u> that the proteins of amino acid sequences 3 and 7 represent a protein having RFS activity, or that a cDNA obtained as described in parts (g) and (h) of claim 1 encodes such a protein.

The Examiner asserts that Richmond et al. indicates that more than sequence similarity is needed as evidence of function, pointing out the paragraph bridging the left and right columns of page 497. Appellants see here only a description of domains present in members of the cellulose synthase family of proteins. Indeed, Richmond might be interpreted as more supportive of Appellants' position that sequence similarity is a useful tool for grouping proteins by activity. The Board might take note of Figure 1 of the paper, showing assignment of members of the family to subfamilies CesA, CesB, CesD, etc. based upon a molecular phylogeny. The Board may usefully compare Figure 1 of Richmond with Figure 1 attached to the Nagasawa Declaration, which shows a similar molecular phylogeny among RFSs, STSs and a SIP, with the result of clear separation of the three groups of enzymes.

The Examiner points out the last paragraph of Duggleby. There, the author states, "Ultimately the function of any DNA sequence, whose identity is based solely on homology, can only be proven by experiments designed to evaluate that function." Again, this simply goes to the standard of the proof. For purposes of alleging utility in a patent application, the standard of proof is merely the preponderance of the evidence. Appellants note that Duggleby has no problem asserting function from sequence similarity. The Board might consider the text of the Note Added In Proof: "Recent examination of GenBank expressed sequence tags has identified three sequences ... that may represent higher plant ALS small subunits. The last of these gives a very good match to the *P. purpurea* sequence; over residues 83-154 there are 46 identical, and 10 similar, amino acids." The Board might further note that the author's conclusion is based upon a degree of identity of only 71% at the amino acid level of a partial amino acid sequence.

The Duggleby paper describes study of the small subunit of the acetolactate synthase (ALS) from a bacterium, yeast and an alga. The paper provides an alignment of the genes from these three organisms (Figure 2). The authors note that there is only "limited similarity" among the three sequences, but nonetheless were able to detect a number of known bacterial ALS genes and also discovered the eukaryotic versions of the gene using a BLAST search of GENBANK and the bacterial sequence (*B. flavum*) as a query. See, p. 247, under Results and Discussion. Thus, Duggleby in fact also supports Appellants' assertion that comparison of sequence data is a common technique in the art for predicting biochemical function of a protein. ("These results clearly indicate that *S. cerevisiae* and *P. purpurea* contain a gene that could encode an ALS small subunit." (at the top of the right column on p. 247.))

Peterbauer (2002) describes isolation of a raffinose synthase gene from *P. sativum* (pea). The Examiner asserts that Peterbauer teaches that RFSs, STSs and SIPs demonstrate high overall sequence homology. This has not been disputed by Appellants. Peterbauer discusses this result in terms of assignment of all three of these enzyme types to the glycoside hydrolase enzyme family (p. 841, right column, above Figure 1). Appellants' argument is that RFSs are more alike, and STSs are more alike, than RFSs resemble STSs and therefore these members of the glycoside hydrolase family are distinguishable subfamilies.

Appellants note that the Examiner has read Peterbauer (2002) rather selectively. At the top of the right column on p. 841, Peterbauer easily distinguishes a STS transcript from a RFS transcript on the basis of sequence identity.

In fact, Peterbauer uses an approach to cloning the pea RFS gene that is similar to that described in the present specification. That is, PCR primers designed from the amino acid sequence of the RFS were used to amplify template DNA from the pea plant. Then the resulting cDNA was expressed in a cell and the protein so produced was assayed for RFS activity. These teachings may usefully be compared with the working examples 1-6 of the present specification and the Watanabe Declaration.

Peterbauer (2002) does not particularly support the Examiner's position. The authors note that, "to distinguish between raffinose synthase and stachyose synthase, the primers were chosen to encompass a block of about 80 amino acids, which is exclusively present in stachyoses synthases." (Top of page 841, right column.) This establishes that there are in fact amino acid sequence elements that serve to distinguish a RFS from a STS. Second, the Examiner has read the paper very selectively, urging the data showing sequence similarity, but ignoring for example, the text at the top of the right column of p. 841, "To isolate a cDNA encoding for raffinose synthase by reverse transcription-PCR, degenerate primers were designed based upon amino acid motifs conserved among *Cucumis sativa* raffinose synthase, stachyose synthase and related sequences." Thus, Peterbauer et al. were satisfied that they could reliably distinguish among such sequences either by biochemical or sequence analysis methods.

Thus, none of the papers proffered by the Examiner in rebuttal of Appellants' arguments is effective to undermine either their argument that the specification is enabling of practice of the invention, or the evidence of the Nagasawa Declaration that one of ordinary skill in the art can readily determine by amino acid sequence analysis whether a given amino acid sequence represents a RFS, a STS or a SIP.

Since the Examiner has in the first instance failed to establish a *prima facie* lack of enablement of the claimed invention, and in the second instance has failed to effectively rebut

Appellants' arguments and evidence offered in support of enablement of the claimed invention, the present rejection of claim 1 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement, must be **reversed**.

VIIB.2. – claim 4

Claim 4 is directed to isolated nucleic acids encoding the amino acid sequence of SEQ ID NO: 3. All of Appellants' arguments against the Examiner's rejection of claim 1 for lack of enablement are applicable as well to claim 4. However, the breadth of this claim is substantially narrower than the breadth of claim 1. Also, the amino acid sequence of SEQ ID NO: 3 is of the complete length of the protein and the degree of sequence identity to SEQ ID NO: 5, proven to represent an enzyme having RFS activity in the Watanabe Declaration, is 63%, substantially higher than the degree of identity between a RFS and STS (*see*, Table 2 attached to Appellants' Amendment of February 11, 2004). Therefore, the degree of unpredictability as to whether SEQ ID NO: 3 encodes a RFS enzyme or not may be considered to be lower than that for claim 1 as a whole, and so enablement of claim 4 should be weighed separately from enablement of claim 1.

For all of the reasons above, Appellants urge that the Examiner's decision that the specification fails to enable claim 4 should be **reversed**.

VIIB.3. – claim 5

Claim 5 is directed to an isolated nucleic acid comprising a recited portion of sequence of SEQ ID NO: 4. All of Appellants' arguments against the Examiner's rejection of claim 1 for lack of enablement are applicable as well to claim 5. However, the breadth of this claim is substantially narrower than the breadth of claim 1. Also, the recited portion of SEQ ID NO: 4 encodes the complete length of SEQ ID NO: 3, a full-length RFS having a degree of sequence identity to SEQ ID NO: 5, proven to represent an enzyme having RFS activity in the Watanabe Declaration, of 63%, substantially higher than the degree of identity between a RFS and STS (*see*, Table 2 attached to Appellants' Amendment of February 11, 2004). Therefore, the degree

of unpredictability as to whether SEQ ID NO: 4 encodes a RFS enzyme or not may be considered to be lower than that for claim 1 as a whole.

Furthermore, the only experimentation necessary to determine conclusively whether the sequence SEQ ID NO: 4 in fact does encode a RFS enzyme is to clone this sequence into an expression vector, transform a bacterial or plant host cell with the vector and test the transformed bacteria or plant tissue for expression of RFS activity in the manner described in the specification. (*See, e.g.* pp. 31-37 of the specification.) Such experimentation must be considered well-guided by the specification and expected by the artisan of ordinary skill, and so not "undue". Accordingly, enablement of claim 5 should be weighed separately from enablement of claim 1.

For all of the reasons above, Appellants urge that the Examiner's decision that the specification fails to enable claim 5 should be **reversed**.

Also, the specification, at page 26, line 13 to page 28, line 21, describes use of nucleic acids of the invention in genotyping analysis or for detection of mutation in raffinose synthase genes or for marking cloned plant varieties. These utilities are independent of whether or not the cloned DNA encodes a protein having raffinose synthase activity, for example, a nucleic acid encoding only a part of a raffinose synthase gene is adequate for use in such methods. At least for genotyping and plant variety identification even nucleic acids unrelated to raffinose synthase genes are useful. Therefore, the Board should consider that the specification provides adequate description of how to use the nucleic acid of claim 5 and the Examiner's decision to the contrary may by **reversed** for this reason alone.

VII.B.5 – Claim 8

Claim 8 is directed to isolated nucleic acids encoding the amino acid sequence of SEQ ID NO: 7. All of Appellants' arguments against the Examiner's rejection of claim 1 for lack of enablement are applicable as well to claim 8. However, the breadth of claim 8 is substantially narrower than the breadth of claim 1. Therefore, the degree of unpredictability as to whether

SEQ ID NO: 8 encodes a RFS enzyme or not may be considered to be lower than that for claim 1 as a whole, and so enablement of claim 8 should be weighed separately from enablement of claim 1.

VII.B.6 – Claim 9

Claim 9 is directed to an isolated nucleic acid comprising a recited portion of sequence of SEQ ID NO: 8. All of Appellants' arguments against the Examiner's rejection of claim 1 for lack of enablement are applicable as well to claim 9. However, the breadth of this claim is substantially narrower than the breadth of claim 1. Therefore, the degree of unpredictability as to whether SEQ ID NO: 8 encodes a RFS enzyme or not may be considered to be lower than that for claim 1 as a whole, and so enablement of claim 9 should be weighed separately from enablement of claim 1.

Furthermore, the only experimentation necessary to determine conclusively whether the sequence SEQ ID NO: 8 in fact does encode a RFS enzyme is to clone this sequence into an expression vector, transform a bacterial or plant host cell with the vector and test the transformed bacteria or plant tissue for expression of RFS activity in the manner described in the specification. (*See, e.g.* pp. 31-37 of the specification.) Such experimentation must be considered well-guided by the specification and expected by the artisan of ordinary skill and so not "undue". Accordingly, the Board should weigh enablement of claim 9 separately from enablement of claim 1.

For all of the reasons above, Appellants urge that the Examiner's decision that the specification fails to enable claim 9 should be **reversed**.

Also, the specification, at page 26, line 13 to page 28, line 21, describes use of nucleic acids of the invention in genotyping analysis or for detection of mutation in raffinose synthase genes or for marking cloned plant varieties. These utilities are independent of whether or not the cloned DNA encodes a protein having raffinose synthase activity, for example, a nucleic acid encoding only a part of a raffinose synthase gene is adequate for use in such methods. At least

for genotyping and plant variety identification even nucleic acids unrelated to raffinose synthase genes are useful. Therefore, the Board should consider that the specification provides adequate description of how to use the nucleic acid of claim 9 and the Examiner's decision to the contrary may by **reversed** for this reason alone.

VII.B.7 – Claim 10

Claim 10 is directed to an isolated nucleic acid comprising the entirety of any one of SEQ ID Nos: 4, 6 or 8. All of Appellants' arguments against the Examiner's rejection of claim 1 for lack of enablement are applicable as well to claim 10. However, the breadth of this claim is substantially narrower than the breadth of claim 1. Therefore, the degree of unpredictability as to whether SEQ ID Nos: 4 and 8 encode a RFS enzyme or not may be considered to be lower than that for claim 1 as a whole, and so enablement of claim 10 should be weighed separately from enablement of claim 1.

Furthermore, the only experimentation necessary to determine conclusively whether the sequences SEQ ID NO: 4 and 8 in fact do encode a RFS enzyme is to clone these sequences into an expression vector, transform a bacterial or plant host cell with the vector and test the transformed bacteria or plant tissue for expression of RFS activity in the manner described in the specification. (*See, e.g.* pp. 31-37 of the specification.) Such experimentation must be considered well-guided by the specification and expected by one of ordinary skill in the art and so not "undue". Accordingly, the Board should weigh enablement of claim 10 separately from claim 1.

For all of the reasons above, Appellants urge that the Examiner's decision that the specification fails to enable claim 10 should be **reversed**.

Also, the specification, at page 26, line 13 to page 28, line 21, describes use of nucleic acids of the invention in genotyping analysis or for detection of mutation in raffinose synthase genes or for marking cloned plant varieties. These utilities are independent of whether or not the cloned DNA encodes a protein having raffinose synthase activity, for example, a nucleic acid

encoding only a part of a raffinose synthase gene is adequate for use in such methods. At least for genotyping and plant variety identification even nucleic acids unrelated to raffinose synthase genes are useful. Therefore, the Board should consider that the specification provides adequate description of how to use the nucleic acid of claim 10 and the Examiner's decision to the contrary may by **reversed** for this reason alone.

VII.C.8 – Claims 16-23, 28 and 29

Claims 16-23, 28 and 29 are dependent ultimately from claim 1 and stand rejected for the same reasons as claim 1 is rejected. These dependent claims are directed to embodiments of the invention in which a nucleic acid providing a sequence encoding a RFS enzyme is operatively linked to a promoter (claim 16) or placed into a vector (claim 17) or to a transformed host cell comprising the nucleic acid of claim 1 either *per se,* or as part of a promoter-structural gene construct or as part of a vector (claims 18, 19 and 20, respectively). Claims 22, 23, 28 and 29 further define the nature of the host cell or the nature of the promoter, respectively.

The Examiner has so far presented no reason for rejection of claims 16-23, 28 and 29 independent from the rejection of claim 1. Thus, the Board is respectfully requested to consider that, should the decision of the Examiner with respect to any part (a) through (h) of claim 1 be reversed, the dependent claims 16-23, 28 and 29 should be indicated as allowable if rewritten to recite the allowable part of claim 1.

VII.C. – Summary and Conclusion

Claims 1, 4, 5, 8-10, 16-23, 28 and 29 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description of the invention. The Examiner's argument on this issue is that the specification fails to describe any particular amino acid sequence that defines a protein as having raffinose synthase activity, and therefore the generic invention is not described.

Appellants submit that this argument is not persuasive. In the first instance, the specification asserts that the defined sequences in SEQ ID Nos: 1-8 (of which SEQ ID Nos:3-8 are recited in claims) define nucleic acids according to the invention, either at the nucleic acid or at the amino acid level. Appellants submit that specific description of a structure constitutes substantial evidence that they "possess" the invention so described and have placed such an invention in the hands of the public. *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991).

Furthermore, the specification describes a number of PCR primers, derived from the data of SEQ ID Nos: 2, 4, 6 and 8 or otherwise, that are useful when applied to template nucleic acids from plant types associated with the primer sequences as described in the specification, to obtain further cloned cDNAs encoding raffinose synthase enzymes. The specification also describes how to test any nucleic acids obtained by such a technique for activity of a raffinose synthase. Therefore, the invention is at the very least well-described in "product-by-process" terms. *Fiers v. Revel*, 25 USPQ2d at 1605. One may also consider that the PCR primers represent minimal nucleotide sequences that must be present to define a nucleic acid as one encoding a raffinose synthase. Also, the specification, at pages 20-21, describes particular regions of amino acid sequence that should have high homology to SEQ ID NO: 3, which is an amino acid sequence shown by Declaration evidence to represent a protein having RFS activity. Therefore, to this degree at least, a "structure-function" relationship is described in the specification.

Thus, Appellants submit that the specification meets the legal standard for adequate written description of the claimed invention, *i.e.* it evidences that the inventors were in possession of the invention as claimed. Accordingly, the rejection of claims 1, 4, 5, 8-10, 16-23, 28 and 29 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support, should be reversed.

Claims 1, 4, 5, 8-10, 16-23, 28 and 29 are also are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Examiner's position is essentially that, since one of ordinary skill in the art is unable to distinguish a nucleic acid encoding a raffinose synthase enzyme from a nucleic acid encoding a stachyose synthase enzyme based only on a degree of

sequence identity, the specification fails to teach the skilled artisan how to use the present invention.

This rejection fails in the first instance because the Examiner fails to establish any *prima facie* lack of enablement. Proper consideration of the question of enablement requires establishing that undue experimentation is required to practice the full scope of the invention. This question is addressed by considering a number of factors. *In re Wands*, 8 USPQ2d at 1400.

However, the Examiner's explanation of the rejection addresses only the question of whether one of ordinary skill in the art, having a particular nucleic acid in hand, can predict, based upon its sequence, whether or not that nucleic acid encodes a raffinose synthase enzyme, or whether instead it encodes a stachyose synthase. Such analysis ignores the other factors to be considered.

On the other hand, Appellants explain that the specification is enabling of the claimed invention, addressing the remaining considerations required under *Wands*. Appellants also present evidence to support an allegation that the skilled artisan, using the teachings of the specification in a manner accepted in the art at the time the invention was made (*e.g.* molecular phylogeny based upon degree of amino acid sequence similarity) can easily distinguish a raffinose synthase enzyme from a stachyose synthase enzyme. Appellants also point out that the specification provides express guidance of how to determine biochemically if a protein expressed from a cloned nucleic acid exhibits activity of a raffinose synthase. Furthermore, as to claims 5, 9 and 10, directed to particular nucleic acids encoding raffinose synthase enzymes, the specification describes utilities for the cloned nucleic acids that are independent of whether they actually encode a functional enzyme. For these three claims, the Examiner's entire rationale for making the rejection fails. Therefore it is plainly established that the present specification is enabling of the claimed invention and so the rejection of claims 1, 4, 5, 8-10, 16-23, 28 and 29 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement, must be reversed.

The favorable action of reversal of all of the rejection of claims 1, 4, 5, 8-10, 16-23, 28 and 29 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description support and

for alleged lack of enablement, and remand to the Examiner for allowance of all of the pending claims, is respectfully requested.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A. The claims in Appendix A are as addressed by the Examiner in the Final Office Action of August 23, 2006.

IX. EVIDENCE

A copy of evidence pursuant to §§ 1.130, 1.131, or 1.132 and/or evidence entered by or relied upon by the examiner that is relevant to this appeal is attached hereto as Appendix B.

1. Tables 1 and 2 and Figure. 1, which were presented attached to Appellants' paper of February 11, 2004.

2. Watanabe Declaration, presented attached to Appellants' paper of February 11, 2004

3. Exhibit 1, explanation of various sequence analysis programs, attached to Appellants' paper of November 15, 2004.

4. Lehle and Tanner, *Eur. J. Biochem.* 38:103-110 (1973), cited at the bottom of page 31 of Specification.

5. Declaration of Akistu NAGASAWA, copied from the copending application 09/301,714 and attached to Appellants' paper of June 2, 2006.

6. Richmond et al., *Plant Physiol.* 124:495-498 (2000), cited by the Examiner in the Office Action of August 11, 2003.

7. Duggleby, *Gene* 190:245-249 (1997), cited by the Examiner in the Office Actions of February 6, 2002 and November 20, 2002.

8. Bowie et al., *Science* 247:1306-1310 (1990), cited by the Examiner in the Office Action of November 20, 2002.

9. Lazar et al., *Molecular, Cellular Biology* 8:1247-1252 (1988), cited by the Examiner in the Office Action of November 20, 2002.

10. Broun et al., *Science* 282:1315-1317 (1998), cited by the Examiner in the Office Action of November 20, 2002.

11. Peterbauer et al., *Planta* 215:839-846 (2002), cited by the Examiner in the Office Action of August 11, 2003 and December 2, 2005.

12. Exhibit 4, alignment of SEQ ID NO: 5 of the instant application with SEQ ID NO: 7 of the instant application.

X. RELATED PROCEEDINGS

There are no prior decisions of any Court or of the Board of Appeals and Interferences in this matter.

Dated: September 24, 2007

Respectfully submitted,

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APPENDIX A

Claims Involved in the Appeal of Application Serial No. 09/301,766

The pending claims 1, 4-10, 16-23, 28 and 29, are set forth below as amended on June 2, 2006. Claims 6 and 7 are allowed. **Claims 1, 4, 5, 8-10, 16-23, 28 and 29 are on appeal**:

1. An isolated nucleic acid which comprises a polynucleotide encoding a protein that binds a D-galactosyl group through the α(1→6) bond to the hydroxyl group attached to the carbon atom at 6-position of the D-glucose residue in a sucrose molecule to form raffinose, wherein said polynucleotide comprises a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NO: 3,

(b) a nucleotide sequence depicted by the 236th to 2584th nucleotides in the nucleotide sequence as depicted in SEQ ID NO: 4,

(c) a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NO: 5,

(d) a nucleotide sequence depicted by the 134th to 2467th nucleotides in the nucleotide sequence as depicted in SEQ ID NO: 6,

(e) a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NO: 7,

(f) a nucleotide sequence depicted by the 1st to 1719th nucleotides in the nucleotide sequence as depicted in SEQ ID NO: 8,

(g) a nucleotide sequence obtained from a polynucleotide which is amplified from a nucleic acid obtained from beet with a combination of a PCR primer selected from the group consisting of SEQ ID NO: 11 and SEQ ID NO: 13 and a PCR

primer selected from the group consisting of SEQ ID NO: 12 and SEQ ID NO: 14, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of (a) or (b), in a buffer comprising 0.9M NaCl and 0.09M citric acid at 65°C to 68°C, and

(h) a nucleotide sequence obtained from a polynucleotide which is amplified from a nucleic acid obtained from mustard or rapeseed with a combination of a PCR primer selected from the group consisting of SEQ ID NO: 15, SEQ ID NO: 17 and SEQ ID NO: 19 and a PCR primer selected from the group consisting of SEQ ID NO: 16, SEQ ID NO: 18 and SEQ ID NO: 20, wherein said nucleotide sequence hybridizes with a nucleotide sequence complementary to the nucleotide sequence of any one of (c) to (f), in a buffer comprising 0.9M NaCl and 0.09M citric acid at 65°C to 68°C.

4. An isolated nucleic acid comprising a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NO: 3.

5. An isolated nucleic acid comprising the nucleotide sequence depicted by the 236th to 2584th nucleotides in the nucleotide sequence as depicted in SEQ ID NO: 4.

6. (Allowed) An isolated nucleic acid comprising a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NO: 5.

7. (Allowed) An isolated nucleic acid comprising the nucleotide sequence depicted by the 134th to 2467th nucleotides in the nucleotide sequence as depicted in SEQ ID NO: 6.

8. An isolated nucleic acid comprising a nucleotide sequence encoding the amino acid sequence as depicted in SEQ ID NO: 7.

9. An isolated nucleic acid comprising the nucleotide sequence depicted by the 1st to

1719th nucleotides in the nucleotide sequence as depicted in SEQ ID NO: 8.

10. An isolated nucleic acid comprising the nucleotide sequence as depicted in SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8.

16. An isolated nucleic acid comprising the nucleic acid of claim 1, which is operatively linked to a promoter.

17. A vector comprising the nucleic acid of claim 1.

18. A transformant, wherein the nucleic acid of claim 1 is introduced into a host cell.

19. A transformant, wherein the nucleic acid of claim 16 is introduced into a host cell.

20. A transformant, wherein the vector of claim 17 is introduced into a host cell.

21. The transformant of claim 18, wherein the host cell is a microorganism.

22. The transformant of claim 18, wherein the host cell is a plant cell.

23. A method for producing a raffinose synthase which comprises the steps of: culturing or growing the transformant of claim 18 to produce the raffinose synthase, and collecting the raffinose synthase.

28. The nucleic acid of claim 16, wherein said promoter is effective in a plant cell.

29. The nucleic acid of claim 16, wherein said promoter is effective in a yeast cell.

APPENDIX B

The following items are of record as evidence in the present application and are attached hereto in support of Appellants' Appeal Brief:

1. Tables 1 and 2 and Figure. 1, which were presented attached to Appellants' paper of February 11, 2004.

2. Watanabe Declaration, presented attached to Appellants' paper of February 11, 2004

3. Exhibit 1, explanation of various sequence analysis programs, attached to Appellants' paper of November 15, 2004.

4. Lehle and Tanner, *Eur. J. Biochem.* 38:103-110 (1973), cited at the bottom of page 31 of Specification.

5. Declaration of Akistu NAGASAWA, copied from the copending application 09/301,714 and attached to Appellants' paper of June 2, 2006.

6. Richmond et al., *Plant Physiol.* 124:495-498 (2000), cited by the Examiner in the Office Action of August 11, 2003.

7. Duggleby, *Gene* 190:245-249 (1997), cited by the Examiner in the Office Actions of February 6, 2002 and November 20, 2002.

8. Bowie et al., *Science* 247:1306-1310 (1990), cited by the Examiner in the Office Action of November 20, 2002.

9. Lazar et al., *Molecular, Cellular Biology* 8:1247-1252 (1988), cited by the Examiner in the Office Action of November 20, 2002.

10. Broun et al., *Science* 282:1315-1317 (1998), cited by the Examiner in the Office Action of November 20, 2002.

11. Peterbauer et al., *Planta* 215:839-846 (2002), cited by the Examiner in the Office Action of August 11, 2003 and December 2, 2005.

12. Exhibit 4, alignment of SEQ ID NO: 5 of the instant application with SEQ ID NO: 7 of the instant application, attached to the present Appeal Brief.